PATENT
Docket No. 295002005025

CERTIFICATE OF HAND DELIVERY

I hereby certify that this correspondence is being hand filed with the United States Patent and Trademark Office in Washington, D.C. on October 18, 1999.

R. Lynn Cruz

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the application of:

Irving BOIME et al.

Serial No.: 08/918,288

Filing Date: 25 August 1997

For: SINGLE-CHAIN FORMS OF THE GLYCOPROTEIN HORMONE QUARTET

Examiner: L. Spector

Group Art Unit: 1646

DECLARATION OF ELLIOT L. ELSON PURSUANT TO 37 C.F.R § 1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

I, Elliot L. Elson, declare as follows:

1. I am professor of Biochemistry and Molecular Biophysics at Washington University. I am a practitioner in the field of protein chemistry and protein physical characteristics. A copy of a summary of my curriculum vitae is attached as Exhibit A.

2. I understand that an issue has arisen in the above-referenced case relating to the predictability of success in maintaining biological activity when the subunits of a multimeric protein are prepared as a single fusion protein. I understand that the Patent Office has cited the disclosure of a patent to Thomason, U.S. Patent No. 5,705,484, which describes a single-chain form of a protein belonging to the platelet-derived growth factor (PDGF) family. The subunits which make up the PDGF multimers are held together through disulfide bonds. The

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glycoprotein hormones which are the subject of the invention in the above-referenced application are, on the other hand, noncovalently associated subunits.

3. Linking together the subunits of any multimer distorts, to a certain extent, the conformation that would have been obtained had the subunits been associated in a normal manner. Thus, it is, as a general matter, impossible to predict that successful results obtained with similar proteins will extrapolate successfully to dissimilar ones. While it is reasonable to conclude that success with one member of a closely related family will also be achieved with three closely related family members, it is entirely unpredictable whether this success would carry over to unrelated proteins.

4. This unpredictability applies even among unrelated multimers which share the property that their subunits are covalently linked by disulfide bonds. The unpredictability is much higher when one attempts to predict, from results for this group, to those obtained when the subunits are noncovalently linked. This is due to the fact that the distortion caused by the construction of the multimer as a single chain is substantially less when the subunits are covalently bonded through disulfides than is the case when they are noncovalently associated. The biological activity is affected by the degree of association of the subunits and the rate of their dissociation. The differences between the native protein and the single-chain forms is much more pronounced in the case of noncovalently associated subunits.

5. Based on the above, I conclude that it cannot be predicted from the apparent success achieved by Thomason with respect to PDGF whether the glycoprotein hormones would or would not maintain their biological activity when prepared in single-chain form.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

Executed at St. Louis, Missouri on _____, 1999.

_____

Elliot L. Elson

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Elson, Elliot L.

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* * * * * * * * * * * * * * * * CAREER INFORMATION * * * * * * * * * * * * *

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Individual cells carry out mechanical activities such as locomotion, phagocytosis, and division. In these and other processes the cell must maintain its shape under imposed stresses or change its shape to move or do work. Similarly, cells in tissues exert forces which establish the organization and mechanical characteristics of the extracellular matrix in which they are embedded. Both cells and matrix contribute to the mechanical properties of tissues. The mechanical properties and functions of cells are governed mainly by the cytoskeleton. The organization of cytoskeletal actin filaments, microtubules, and intermediate filaments is determined by proteins which modulate the lengths of the filaments, their interactions with each other, and their anchorage to other cellular structures. One of our long-range goals is to characterize the functions of cytoskeletal proteins in terms of their effects on cell and tissue mechanical characteristics. We are studying both individual cells and cells in reconstituted tissue models. We have developed methods for measuring the mechanical properties of individual cells in terms of their resistance to indentation and stretch. Measurements on reconstituted tissue models include both contractile force generated by cells in tissues and tissue stiffness, i.e., resistance to stretch. For this latter line of studies we have engineered tissue models using a number of different cells types, including fibroblasts, cardiomyocytes, and vascular smooth muscle cells. We use these tissue equivalents to study not only functions of specific cytoskeletal proteins but also mechanisms of regulation of cellular contractile force, tissue remodeling, and effects of imposed forces on tissue organization and mechanical characteristics.

• actin filaments, cell locomotion, cell mechanics, cytoskeleton, tissue engineering

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